Complete Summary

GUIDELINE TITLE

EFNS guidelines on pharmacological treatment of neuropathic pain.

BIBLIOGRAPHIC SOURCE(S)

Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P, EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006 Nov;13(11):1153-69. [147 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

The European Federation of Neurological Societies (EFNS) Task Force plans to update these guidelines in 2 years.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

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SCOPE

DISEASE/CONDITION(S)

Neuropathic pain, including:

- Painful polyneuropathy (PPN)
- Postherpetic neuralgia (PHN)
- Trigeminal neuralgia (TN)
- Central pain (CP)
- Other neuropathic pain conditions

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pharmacology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To examine all the randomised controlled trials (RCTs) performed in the various neuropathic pain conditions
- To evaluate the drug effects on pain symptoms, quality of life, and sleep, and the adverse events
- To propose recommendations based on the results of these trials aiming at helping clinicians in their treatment choice for most neuropathic pain conditions
- To propose new studies that may help clarify unsolved issues

TARGET POPULATION

Patients with neuropathic pain

INTERVENTIONS AND PRACTICES CONSIDERED

Painful Polyneuropathy

1. First line treatment: gabapentin, pregabalin, tricyclic antidepressants (TCA)
2. Second/third line treatment: lamotrigine, opioids, serotonin-noradrenalin reuptake inhibitors (SNRIs), tramadol

Postherpetic Neuralgia

1. First line: gabapentin, pregabalin, topical lidocaine, TCA
2. Second/third line: capsaicin, opioids, tramadol, valproate

Trigeminal Neuralgia

1. First line: oxcarbazepine, carbamazepine
2. Second/third line: surgery

Central Pain

1. First line: amitriptyline, gabapentin, pregabalin
2. Second/third line: cannabinoids, lamotrigine, opioids

Note: Refer to the "Major Recommendations" field for information on other medications with level C rating and weak/discrepant results with level A/B evidence.

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment in pain relieving and improving quality of life, sleep, and comorbidities
- Side effects of medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force conducted an initial search through the central database in the Cochrane Library. Whenever the Cochrane search failed to find top level studies for a given neuropathic pain condition or a drug which was supposedly active on neuropathic pain, the Task Force expanded the search using Medline and other electronic databases (1966–to date), and checking reference lists published in meta-analyses, review articles, and other clinical reports. Furthermore, to get the most updated information, the task Force also asked all the pharmaceutical companies producing drugs in this field to provide them with studies not yet

published (refer to Appendix A in the original guideline document). Any reports retrieved from these contacts were pooled with the others for selection.

Inclusion and Exclusion Criteria

Included studies complied with the following criteria: (1) randomized or non-randomized but controlled class I or II trials (lower-class studies were evaluated in conditions in which no higher-level studies were available); (2) pain relief considered as a primary outcome and measured with validated scales; (3) minimum sample of 10 patients; (4) treatment duration and follow up clearly specified; (5) treatment assessed in repeated dose settings for at least 1 week; (6) treatment feasible in an outpatient setting (intravenous [i.v.], subcutaneous, or intrathecal therapy or nerve blocks were not considered); (7) evaluating currently used drugs or drugs under clinical phase-III development: (8) including patients with pain secondary to a definite nervous system lesion/disease or idiopathic trigeminal neuralgia [TN]; (9) full paper citations in English, Danish, French, Finnish, German, Italian, Portuguese or Spanish.

Exclusion criteria were duplicated patient series, uncontrolled studies, pain without evidence of a nerve lesion, such as atypical facial pain, Complex Regional Pain Syndrome (CRPS) type I or low back pain, non-validated or unconventional outcome measures, non-pharmacological intervention, treatments acting directly on the disease or pre-emptive treatments.

Information Selected from the Trials

From articles meeting the search criteria, information regarding the efficacy not only on overall pain and main side-effects was extracted, but also effects on pain symptoms or signs, quality of life and mood, whenever available. The Task Force also referred to recent well-conducted meta-analyses when analysis of these studies did not provide with additional information regarding these end-points. The NNT (the number of patients needed to treat to obtain one responder to the active drug) with 95% confidence intervals (CI) for class I/II studies was used in order to gain information regarding the overall efficacy of a drug. Unless otherwise specified, the NNT for 50% pain relief was used. These values were calculated for newer trials or extracted from recent meta-analyses performed by members of this Task Force or the Cochrane database. The Number Needed to Harm was not used because of lack of uniform criteria for assessing harmful events.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Classification of evidence and recommendation grading adhered to the European Federation of Neurological Societies (EFNS) standards. In particular, class I refers not only to adequate prospective randomized controlled trials (RCTs), but also to adequately powered systematic reviews (SRs) (see the "Availability of Companion Documents" field and "Rating Scheme for the Strength of the Evidence" field).

The NNT (the number of patients needed to treat to obtain one responder to the active drug) with 95% confidence intervals (CI) for class I/II studies was used in order to gain information regarding the overall efficacy of a drug.

Unless otherwise specified, the NNT for 50% pain relief was used. These values were calculated for newer trials or extracted from recent meta-analyses performed by members of this Task Force or the Cochrane database. The Number Needed to Harm was not used because of lack of uniform criteria for assessing harmful events.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In order to provide the neurologist with clear indications regarding drug treatment for the most studied neuropathic pains, the Task Force decided to produce individual chapters for painful polyneuropathies, postherpetic neuralgia, trigeminal neuralgia, and central pain (spinal cord injury, post-stroke pain, and multiple sclerosis), but to search and report also for the other less studied neuropathic conditions (post-traumatic/post-surgical nerve lesions, phantom limb pain, Guillain–Barre´ syndrome) and for neuropathic pains with multiple aetiology. Each chapter was assigned to two Task Force participants.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents" field in this summary).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Painful Polyneuropathy

Treatments with established efficacy on the basis of class I trials in painful polyneuropathy (PPN) (with the exception of human immunodeficiency virus (HIV)-associated polyneuropathy) are tricyclic antidepressants (TCAs), duloxetine, venlafaxine, gabapentin (GBP), pregabalin, opioids and tramadol (**level A**). The balanced TCA (amitriptyline and imipramine) at adequate dosages seem to have the highest efficacy on the basis of NNT (the number of patients needed to treat to obtain one responder), but most data stem from small trials which may overestimate efficacy. The Task Force recommends TCA or GBP/pregabalin as first choice. The serotonin-noradrenaline reuptake inhibitors (SNRI) duloxetine and venlafaxine are considered second choice because of moderate efficacy, but are safer and have less contraindications than TCAs and should be preferred to TCA particularly in patients with cardiovascular risk factors (see the "Potential Harms" field). Second/third-line therapy includes opioids (potential safety concerns in noncancer pain; see the "Potential Harms" field) and lamotrigine (LTG) (**level B**). Treatments with weaker/lack of efficacy include capsaicin, mexiletine, oxcarbazepine (OXC), selective serotonin reuptake inhibitors (SSRIs), topiramate (**level A**), memantine, mianserin and topical clonidine (**level B**). There is low strength of evidence and safety concerns for carbamazepine (CBZ) (see the "Potential Harms" field) (**level C**) and limited support for the use of dextromethorphan and levodopa. Discrepant results have so far been obtained with valproate.

HIV-Associated Neuropathy and Chemotherapy-Induced Neuropathy

HIV-associated polyneuropathy has been found refractory to most currently assessed drugs. This may be due to particular mechanisms of pain in this often progressive condition and/or to a high placebo response, observed in many trials. Only LTG has been reported efficacious in a subgroup of patients receiving antiretroviral therapy (ART) in one class I trial, but a smaller class II trial reported totally opposite results (**level B**).

Postherpetic Neuralgia

In postherpetic neuralgia (PHN), drugs with established efficacy include TCAs, GBP, pregabalin and opioids (**level A, class I trials**). Drugs with lower efficacy or limited strength of evidence include capsaicin, tramadol, topical lidocaine, and valproate (**level B**). The Task Force recommends TCAs or GBP/pregabalin as first line. Topical lidocaine has been evaluated only in patients with allodynia in short-term studies which used an enrichment phase or were post-hoc analyses from larger trials. However, due to excellent tolerability, this treatment may be preferred in the elderly, particularly in patients with allodynia and small area of pain. Despite established efficacy, strong opioids should be recommended as second choice (see the "Potential Harms" field). Drugs with weak efficacy or inefficacy include mexiletine, lorazepam, and N-methyl-D-aspartate receptor (NMDA) antagonists (**level A**).

Trigeminal Neuralgia

The two most widely used drugs in idiopathic trigeminal neuralgia (TN) are CBZ (200 to 1200 mg/day) (**level A**) and OXC (600 to 1800 mg/day) (**level B**). OXC has a lower strength of evidence than CBZ, but poses less safety concerns. Baclofen and LTG have only **level C evidence**. The Task Force recommends CBZ or OXC as first line. Because TN typically lasts forever with periods of partial or complete remission and recurrence, the patients should be taught to adapt the dosage to the frequency of attacks. There is no evidence that combination therapies are advantageous. In patients non-responsive to medical treatment, surgical interventions have given excellent results. In fact, many patients cannot withstand several weeks of pharmacological testing and need prompt neurosurgical attention. Baclofen or LTG may be proposed as add on in patients refractory to CBZ or OXC, particularly if the patient cannot undergo or refuses surgery.

The task Force encourages controlled studies in symptomatic TN.

Central Pain

Considering the small number of randomised controlled trials (RCTs) in central pain (CP) and the generally small sample sizes, the treatment may be based on general principles for peripheral neuropathic pain treatment and for side-effect profile. There is **level B** evidence for the use of LTG, GBP, pregabalin (unpublished study) or tricyclic antidepressants for post-stroke or spinal cord injury (SCI) pain. The level of evidence is lower for opioids in the lack of placebo-controlled studies (**level C**). There is **level B evidence** for inefficacy of valproate and mexiletine in SCI pain. In CP associated with multiple sclerosis (MS), cannabinoids have shown significant efficacy (**level A**), but may raise safety concerns (see the "Potential Harms" field). Therefore, the Task Force recommends initially a trial with other drugs found effective on other CP conditions.

Less Studied Neuropathic Pain Conditions

Several less studied neuropathic conditions, such as phantom limb pain, post-surgical neuropathic pain, and Guillain–Barre syndrome, appear to be similarly responsive to most current drugs used in other neuropathic conditions (e.g. TCAs, GBP, opioids), but results are based on a limited number of generally **class II** RCTs with small sample sizes (**level B**). Neuropathic pain due to cancer infiltration seems to be more refractory to drug treatment, probably because it is a progressive condition.

Final Recommendations and Issues of Future Trials

Selecting a first-line medication in neuropathic pain should take into account not only the relative efficacy based at best on direct drug comparisons, but also the ratio efficacy/safety. The effect on different pain symptoms, comorbidities and quality of life should also be documented. So far, such assessment has been performed in a small number of studies for a few drugs only, and the evaluation of symptoms and signs used sometimes inadequate or non-validated methods.

The effects of drugs on distinct peripheral neuropathic conditions share many similarities, with the exceptions of HIV-polyneuropathy and TN. Central pain has been much less studied. For this reason, the following recommendations concern mainly peripheral neuropathic pain. Recommendations pertaining to other conditions can be found in the above sections and Table below.

Drugs with best established efficacy in various neuropathic conditions and recommended as first line include TCA, GBP and pregabalin (**level A, several class I trials**). TCA seem to be more efficacious on the basis of NNT, but these values may have been overestimated and their superiority has generally not been confirmed by substantial head-to-head comparative trials. These drugs have cardiac effects and should be used cautiously in elderly patients. Drugs with less established efficacy in various neuropathic conditions and recommended as second line include topical lidocaine, the SNRI venlafaxine and duloxetine, LTG and tramadol. However, topical lidocaine may be preferred in patients with PHN or focal neuropathy and small area of pain, particularly in the elderly. Contrary to common notion about their poor efficacy in neuropathic pain, opioids have been found efficacious in several class I trials in various neuropathic conditions (**level A**) but should only be proposed second to third line in chronic non-cancer pain. There is insufficient support for the use of CBZ and OXC (with the noteworthy exception of TN), capsaicin (with the exception of PHN), mexiletine, NMDA antagonists, SSRI, topiramate, because of weak efficacy, discrepant results or safety concerns. Despite long-term use of valproate for epilepsy, RCTs have only recently appeared with this drug in peripheral neuropathic pain with good efficacy in several class II studies from the same group, but negative results from another group. This drug needs further trials by other groups before its level of recommendation is settled.

Regarding comorbidities or quality of life, only GBP, pregabalin and duloxetine have been adequately studied with positive effects, and may therefore be preferred in patients with severe impact of pain on quality of life or significant comorbidities (**level A**), whilst lack of effects of opioids on these outcomes have been reported in most trials. Regarding pain symptoms or signs, only antidepressants and opioids/tramadol have so far been shown effective on ongoing and paroxysmal pain, whilst effects on brush-induced allodynia have been reported for topical lidocaine and opioids/tramadol (**level B**). The use of topical lidocaine may be preferred in patients with mechanical allodynia.

Combination therapy may be proposed in cases of insufficient efficacy with monotherapy and should preferably use drugs with complementary mechanisms of action. It has been shown useful so far for GBP/morphine (**level A**).

Table Classification of Evidence for Drug Treatments in Painful Polyneuropathy (PPN), Postherpetic Neuralgia (PHN), Trigeminal Neuralgia (TN), and Central Pain, with Recommendations for First- and Second-line Treatments

Pain Condition	Level A Rating	Level B Rating	Level C Rating or Weak/Discrepant Results with Level A/B Evidence	Recommendations for First Line	Recommendations for Second or Third Line

Pain Condition	Level A Rating	Level B Rating	Level C Rating or Weak/Discrepant Results with Level A/B Evidence	Recommendations for First Line	Recommendations for Second or Third Line
PPN	Gabapentin Opioids[1] Pregabalin SNRI TCA Tramadol	Lamotrigine	Capsaicin, topical CBZ Levodopa Mexiletine NMDA antagonists OXC SSRI[2] Topiramate Valproate	Gabapentin Pregabalin TCA	Lamotrigine Opioids SNRI Tramadol
PHN	Gabapentin Opioids[3] Pregabalin TCA	Capsaicin, topical Lidocaine, topical Tramadol Valproate	NMDA antagonists Lorazepam Mexiletine	Gabapentin Pregabalin Lidocaine, topical (in patients with small area of pain-allodynia) TCA	Capsaicin Opioids Tramadol Valproate
TN	CBZ	OXC	Baclofen Lamotrigine	OXC CBZ	Surgery
Central pain		Cannabinoids[4] (in MS) Gabapentin (in SCI) Pregabalin[5] (in SCI) Amitriptyline (in CPSP) Lamotrigine (in CPSP)	Mexiletine Opioids[6] (in multiple-aetiology pains) Valproate	Amitriptyline Gabapentin Pregabalin	Cannabinoids[4] Lamotrigine Opioids

Recommendations take into account not only the efficacy assessed in class I or II trials, but also the side-effect profile and safety issues (drugs appear in alphabetical order).

TCA have level A evidence for efficacy but should be used cautiously in elderly patients particularly with cardiac risks. Opioids (level A evidence for use in several neuropathic pain conditions) are recommended second/third line because of potential safety concerns in chronic neuropathic noncancer pain, particularly for long-term use [111]. SNRI (duloxetine and venlafaxine, level A in PPN) are recommended second line because of a comparatively lower efficacy, but may be preferred to TCA particularly in patients with cardiovascular risk factors. Lidocaine patches (level B evidence) may be proposed first line in patients with small area of pain and allodynia, particularly in the elderly, because of excellent tolerability. Lamotrigine, due to potentially severe cutaneous rashes, is recommended second/third line. Oxcarbazepine (OXC, level B evidence) is proposed first line in trigeminal neuralgia, because of lower safety concerns than for carbamazepine (CBZ). Very few trials have been performed in central pain and recommendations are generally based on level B evidence for most treatments.

1. Oxycodone
2. On the basis of one RCT each, paroxetine has been found moderately effective and citalopram and fluoxetine ineffective.
3. Oxycodone, morphine and methadone
4. Cannabinoids, due to potential safety concerns, should be used after a negative trial with other drugs found beneficial in other central pain conditions.
5. Pregabalin has been studied in a still unpublished trial in SCI.

6. Levorphanol (controlled study, but no placebo group)

Abbreviations

CBZ, carbamazepine; Complex Regional Pain Syndrome (CRPS); MS, multiple sclerosis; NMDA, N-methyl-D-aspartate receptors; OXC, oxcarbazepine; PHN, postherpetic neuralgia; PPN, painful polyneuropathy; SCI, spinal cord injury; SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TN, trigeminal neuralgia

Definitions:

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate pharmacological treatment of neuropathic pain

POTENTIAL HARMS

Adverse Effects of Medications

- The most common side-effects of tricyclic antidepressants (TCA) are dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary hesitation. More selective TCA such as nortriptyline are better tolerated than the non-selective ones, with less anticholinergic effects and sedation. A suspected association between TCA treatment and sudden cardiac death has raised concern; a recent epidemiological study found a slight increase in sudden cardiac death with TCA doses superior to 100 mg/day. Therefore caution is recommended for older patients, particularly those with cardiovascular risk factors.
- Serotonin-noradrenaline reuptake inhibitors (duloxetine, venlafaxine) are safer to use than TCAs and are a better option in patients with cardiac disease. The relative risk for withdrawal due to side-effects is weak and there is no need for drug level monitoring. The most frequently observed adverse events with duloxetine are nausea, vomiting, constipation, somnolence, dry mouth, increased sweating, loss of appetite and weakness. Although immediate release venlafaxine is associated with adverse central nervous system (CNS) and somatic symptoms such as agitation, diarrhoea, increased liver enzymes, hypertension and hyponatremia the extended release formulation seems to be far more tolerable, the main side-effects being gastrointestinal disturbances
- Carbamazepine (CBZ) entails frequent adverse events, which include sedation, dizziness, gait abnormalities. Liver enzymes, blood cells, platelets and sodium levels must be monitored for at least during 1 year, because of possible risk for hepatitis-anaplastic effects or hyponatremia. Induction of microsomal enzyme systems may influence the metabolism of several drugs. In contrast to CBZ, oxcarbazepine (OXC) does not entail enzymatic induction and there is little risk for crossed cutaneous allergy. In the first months of treatment, sodium levels must be monitored because OXC, like CBZ induces hyponatraemia, particularly in the elderly (6% in a cohort of 54 patients). As

regards other side-effects, although a better tolerance has been claimed with OXC compared with CBZ, this notion lacks consistent evidence from class I trials. In a recent trial in diabetic painful polyneuropathy, 27.5% of the OXC group discontinued treatment due to central or gastrointestinal side-effects versus 8% with the placebo.

- The most common side-effects of gabapentin (GBP) and pregabalin include dizziness, somnolence, peripheral oedema, and dry mouth, with a similar frequency for both drugs. Whilst GBP is widely accepted as highly tolerable even at high dosages (>2400 mg), the reports on pregabalin change remarkably with the daily dose: with 150 to 300 mg there is almost no difference with placebo, whilst the withdrawal rate reaches 20% with 600 mg.
- Lamotrigine is generally well tolerated. Side-effects include dizziness, nausea, headache and fatigue. However, it may induce potentially severe allergic skin reactions. Lamotrigine should not be used in combination with valproate.
- The most common side-effects of opioids are constipation, sedation, nausea, dizziness and vomiting. The risk of cognitive impairment has been reported to be negligible, although morphine may impair attention at very high dosages. Tramadol has been reported to induce dizziness, dry mouth, nausea, constipation and somnolence with significantly more dropouts compared with placebo. There is an increased risk of seizures in patients with a history of epilepsy or receiving drugs which may reduce the seizure threshold. Serotonergic syndrome (various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, fever, nausea, diarrhoea, flushing, and rarely, rhabdomyolysis and death) may occur if tramadol is used as an add-on treatment to other serotonergic medications (particularly selective serotonin reuptake inhibitors [SSRIs]).
- The use of lidocaine patches is very safe with a very low systemic absorption and only local adverse effects (mild skin reactions).
- Cannabinoids have been found generally well tolerated with low dosages and slow titration. Adverse events are mainly dizziness, dry mouth, and sedation. One study found significant memory impairment with cannabinoids in spray. The potential risk of physical dependence and tolerance warrants consideration with long-term use.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.
- Although well-conducted meta-analyses or systematic reviews on medical treatment of neuropathic pain have been recently published, there is still a lack of expert consensus on guidelines regarding the medical treatment of neuropathic pain. This may be mainly due to the heterogeneity of such pain in terms of aetiologies, symptoms, signs, and underlying mechanisms.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P, EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006 Nov;13(11):1153-69. [147 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Nov

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on the Pharmacological Treatment of Neuropathic Pain

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following authors (initials) did trials or have been consultant for the following pharmaceutical companies:

NA: GlaxoSmithKline, Grunenthal, Novartis, Pfizer, Pierre Fabre, Sanofi-Aventis

GC: GlaxoSmithKline, Lundbeck, Janssen, Novartis, Pfizer

MH: Janssen-Cilag, Merck, Mundipharma, Organon, Orion, Pfizer, Sanofi

PH: Bioschwartz, GlaxoSmithKline, Lundbeck, Pfizer

TSJ: Eli Lilly, GlaxoSmithKline, Grunenthal, Lundbeck, Neurosearch, Pfizer

TN: Allergan, Astra-Zeneca, GlaxoSmithKline, GWPharma, Napp, Novartis, Pfizer, Renovis, SchwarzPharma

SS: Eli Lilly, GlaxoSmithKline, Grunenthal, Lundbeck, Novartis, Pierre Fabre, UCB Pharma

The authors have no other conflicts to declare.

GUIDELINE STATUS

This is the current release of the guideline.

The European Federation of Neurological Societies (EFNS) Task Force plans to update these guidelines in 2 years.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from N. Attal, Centre d'Evauation et de Traitement de la Douleur Hôpital Ambroise Paré, Boulogne-Billancourt, France; Telephone: 33 149 09 4434; Fax: 33 149 09 4435; e-mail: nadine.attal@apr.ap-hop-paris.fr

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.
- Continuing Medical Education questions available from the European Journal of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

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